REMARKS

The Official Action dated February 14, 2000 has been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the Claims

Claims 38 - 65 are in the application.

Claims 38 - 65 have been rejected.

By way of this amendment, claims 43, 46, 49, 52, 55, and 58 have been canceled without prejudice, claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 - 65 have been amended, and new claims 66 - 70 have been added.

Upon entry of this amendment claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 - 70 will be pending.

Summary of the Amendment

The specification has been amended to update the status of the priority and continuing applications.

Applicants respectfully request the Examiner to enter the amendments to the specification (filed February 22, 2000) identifying the nucleotide sequences appearing at page 49, line 39, and at page 50, line 1. Applicants note that at page 2 of the Official Action, the Examiner has referred to an informality in "the sequences on page 52, line 8," but the Applicants believe the Examiner intended to refer to page 53, line 8. The specification has now been amended to provide proper SEQ ID NOS to the sequences appearing at page 53, line 8.

An abstract has also been provided, as required.

Pursuant to 37 C.F.R. §1.85(c), formal drawings will be filed upon a receipt of a Notice of Allowance.

In addition, the specification has been amended to correct other informalities and typographical errors. No new matter has been added.

Claims 38 - 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59 - 65 have been amended to clarify and more accurately describe that which is claimed. Support for these amendments is found throughout the specification (for example, at page 14, lines 21 - 30 and at page 40, lines 30 - 36) and in the claims as originally filed. No new matter has been added.

New claims 66 - 70 have been added to refer to specific embodiments of the invention. Support for new claims 66 - 70 is found in the original claims as filed, and throughout the specification as originally filed, for example, at page 3, line 31 through page 4, line 8, and page 38, line 31 through page 39, line 7. No new matter has been added.

A substitute Sequence Listing is also provided, listing all SEQ ID NOS (1 through 10) appearing in the specification as amended. SEQ ID NOS:1-8 are those listed in the substitute Sequence Listing, filed with the Second Preliminary Amendment of February 22, 2000, which amendment was not entered prior to the present Official Action. Applicants respectfully request that the Examiner insert the currently provided, substitute Sequence Listing in place of the substitute Sequence Listing of February 22, 2000. SEQ ID NOS:1 and 8 are now designated as "artificial" in the Sequence Listing, a designation supported in the specification at page 49, line 37 through page 50, line 3. SEQ ID NOS:9 and 10 identify two amino acid sequence motifs presented at page 53, line 8 of the specification. A paper copy of the substitute Sequence Listing is attached hereto. Also provided is a diskette containing a computer readable form of the substitute Sequence Listing. The information recorded in the computer readable form is identical to the paper copy of the substitute Sequence Listing.

Additionally provided herewith is the unexecuted Declaration of Dr. Giuseppe Del Giudice pursuant to 37 C.F.R. §1.132. The executed Declaration will be forwarded in due course.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 42 - 65 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Examiner objects to the use of the term "substantially" as an allegedly relative term lacking a comparative basis. This term appears in claims 42 (from which claims 43 and 44 depend), 45 (from which claims 46 and 47 depend), 48 (from which claims 49, 50, 51, and 64 depend), 51 (from which claims 52, 53, and 65 depend), 54 (from which claims 55, 56, and 57 depend), claim 57 (from which claims 58 and 59 depend), claim 60 (from which claim 61 depends), claim 61, claim 62 (from which claim 63 depends), and claim 63. The rejection on this basis is rendered moot with respect to claims 43, 46, 49, 52, 55, and 58, which have been canceled without prejudice.

The "distinctly claiming" requirement of 35 U.S.C. §112, second paragraph will be met "if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) *quoting*, *Shatterproof Glass Corp. v. Libbey Owen Ford Co.*, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985). "The term 'substantially' is often used in conjunction with another term to describe a particular characteristic of a claimed invention." M.P.E.P. §2173.05(b). Definiteness will be found for the use of "substantially" where there are general guidelines in the specification (*In re Mattison*, 184 U.S.P.Q. 484 (C.C.P.A. 1975)), or one of ordinary skill in the art would know what was meant by the use of the term (*Andrew Corp. v. Gabriel Electronics*, 6 U.S.P.Q.2d 2010 (Fed. Cir. 1988)).

Applicants assert that the term "substantially" is being used in the claims, as amended, in the context of the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" to describe the non-toxic characteristics of the claimed *H. pylori* polypeptides. One of ordinary skill in the art would understand the phrase

"exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity," as used in the claims, as amended, to describe *H. pylori* polypeptides, including *H. pylori* CAI and heat shock protein, to mean that the polypeptide, or fragment thereof, does not exhibit statistically significant cytotoxic effects, and would thus be acceptable for use in human vaccines. The Declaration of Dr. Del Giudice ("Declaration"), at ¶ 7, further substantiates that the term "substantially," as used to describe the claimed subject matter, provides a definite meaning to one of skill in the art. *In re Alton*, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996). Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2), if this rejection is maintained.

The Examiner further states that the phrase "an effective amount" is allegedly unclear as to the desired effect. All claims containing the phrase "an effective amount" (claims 48, 51, 54, 57, 60, 61, 62, 63, 64, and 65) have now been amended to contain the phrase "an immunologically effective amount." Support for this amendment can be found at page 41, lines 30 - 36 of the specification. Thus, claims 48, 51, 54, 57, 60, 61, 62, 63, 64, and 65 and the claims depending from them, are now clarified in meaning as to the purpose for which the amount is to be effective.

The Applicants respectfully request that the rejection of claims 42 - 65 under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 42 - 65 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors had possession of the claimed invention at the time of filing of the application. Applicants respectfully traverse this rejection.

The written description requirement is designed to ensure that the inventor had possession of the claimed invention at the filing date. *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). "In order to meet the adequate written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the

description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" *In re Alton*, 37 U.S.P.Q.2d at 1581, *citing In re Gosteli*, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). Furthermore, the Examiner bears the burden of "provid[ing] reasons why one of ordinary skill in the art would not consider the description sufficient." *In re Alton*, 37 U.S.P.Q.2d at 1583.

The Examiner has invited Applicants to point to the page and line number in the specification where support for the phrase "exhibits substantially no contribution to toxicity" can be found. As amended, none of the claims contains the phrase "exhibits substantially no contribution to toxicity." Claims 42 and 45, which provide CAI polypeptides, claims 48 and 54, which provide vaccines comprising CAI polypeptides, and claims 60 and 62, which provide methods of making such vaccines, as amended, now recite "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" in the place of the phrase "exhibits substantially no contribution to toxicity." Additionally, claims 51 and 57, which provide vaccines comprising a CAI polypeptide and a second polypeptide of *H. pylori* heat shock protein, and claims 61 and 63, which provide methods of preparing such vaccines, as amended, now recite the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" in place of the phrase "exhibits substantially no contribution to toxicity." Support for the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" can be found in original claim 9 of the application as filed. The specification has been amended accordingly at page 4, line 1, to recite the phrase.

Additionally, new claim 70, which provides a vaccine comprising a CAI polypeptide and a second polypeptide of *H. pylori* cytotoxin (CT), contains the phrase "exhibits substantially no contribution to toxicity." Support for the phrase "exhibits substantially no toxicity, or substantially reduced toxicity" can be found in original claim 8 of the application as filed. The specification has been amended accordingly at page 4, line 1, to recite the phrase. Withdrawal of the rejection on this basis is respectfully requested.

The Examiner has objected to claims which specify "five to about fifteen amino acids," and alleges that the upper limit is not supported in the specification. Claims 44, 47, 50, 53, 56, and 59, as amended, specify a lower limit of "at least about fifteen amino acids." Claims 44, 47, 50, 53, 56, and 59, as amended, therefore, encompass polypeptides of at least 15 amino acids or greater, which is supported in the specification at page 14, lines 21 - 30. Withdrawal of the rejection on this basis is respectfully requested.

The Examiner has rejected claims 42 - 65 and alleges, at page 3 of the Official Action, that the specification

> does not reasonably provide enablement for an amino acid sequence which "exhibits substantially no contribution to toxicity", the "prophylactic or therapeutic vaccine", and the method of treating *H. pylori* infection using said vaccine as recited in the claims.

Applicants respectfully submit that there is insufficient evidence to support the rejection as set forth in the Official Action. Regardless, Applicants respectfully submit that the "Declaration," at ¶ 9 through ¶ 17, provides evidence that one having ordinary skill in the art could practice the claimed invention without undue experimentation. Applicants respectfully submit that the requirements of the first paragraph of 35 U.S.C. §112 have been met.

It is settled law that whenever the adequacy of enablement provided by an applicant's specification is challenged, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. *In re Armbruster*, 185 U.S.P.Q. 152 (C.C.P.A. 1975). The enablement requirement of 35 U.S.C. §112 is satisfied if a disclosure contains sufficient information such that persons of ordinary skill in the art, having the disclosure before them, would be able to make and use the invention. The legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue

experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

The law thus requires that the Patent Office accept Applicants' assertion of enablement or provide reasoning and evidence to substantiate doubts of the objective truth of Applicants' assertion.

Applicants respectfully submit that the reasoning and evidence offered in the Official Action is insufficient to support the conclusion that the claimed invention is not enabled. Moreover, the "Declaration," provided herewith pursuant to 37 C.F.R. §1.132, provides evidence that the invention claimed is enabled. In an effort to clearly put forth the reasons why a conclusion of enablement is proper, Applicants present specific responses to the points raised by the Examiner in making this rejection.

In making her rejection, the Examiner alleges at pages 3 to 4 of the Official Action that

> Applicant[s do] not teach any five, ten or fifteen amino acids of SEQ ID NO:5 which is effective for

> use as a vaccine. The vaccine use implies that the polypeptide would elicit a protective immune response in administered animals when challenged with wildtype *H. pylori*. The state of the prior art does not teach which polypeptides/proteins are effective for use as a vaccine or for the treating of patients infected with *H. pylori*. The current state of the art as of the date of this writing indicates that a mucosal adjuvant is required for vaccine efficacy of *H. pylori* component vaccines. Furthermore, even if a five, ten or fifteen amino acids of SEQ ID NO:5 is effective for use as a vaccine, Applicant provided no guidance as to which amino acids of SEQ ID NO:5 would be effective, or how one skilled in the art would be able to eliminate inoperable embodiments without undue experimentation. Applicant also does not teach which five, ten or fifteen amino acids of SEQ ID NO:5 "exhibits substantially no contribution to toxicity".

Applicants respectfully disagree with the Examiner's characterization of the state of the prior art, and the scope of the disclosure, as well as the requirements for enablement. Applicants further assert that the teachings in the specification provide enablement for the invention as claimed, because they provide enough direction to one of skill in the art to make and use the invention. It would have been routine, at the time the application was filed, to determine which ten or fifteen amino acids of a *H. pylori* protein would be effective in a vaccine. The "Declaration," at ¶ 10 and at ¶ 13 and ¶ 15 through ¶ 17, attests to the routine nature of determining which fragments of ten or fifteen amino acids of a *H. pylori* protein would be effective in a vaccine. At ¶ 10, the "Declaration" explains that it would have been routine to generate fragments of ten or fifteen amino acids of a *H. pylori* protein, using known recombinant techniques and the sequence information disclosed in the specification. At ¶ 13, ¶ 15, and ¶ 16, the "Declaration" describes the many animal models known at the time of filing that could have been used for routine testing of the vaccine efficacy of fragments of *H. pylori* proteins. At ¶ 17, the "Declaration" describes Ghiara *et al.*, 1997 (Exhibit F) which

shows the use of a mouse model of *H. pylori* infection to demonstrate therapeutic and prophylactic vaccine efficacy of full-length CT and CAI proteins. Fragments can be tested similarly to determine which would be effective in a vaccine.

Contrary to the Examiner's assertion, a mucosal adjuvant is not required for the generation of effective *H. pylori* component vaccines. The evidence of PCT application PCT/IB99/00851 (Exhibit G), provided with the "Declaration," at ¶ 18 and ¶ 19, shows that mucosal delivery is not required for effective *H. pylori* component vaccines, much less a mucosal adjuvant, and that intramuscular immunization provides effective protection against infection.

Applicants assert that the determination of which regions of CAI and heat shock proteins "exhibit no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" could have been readily performed by those of skill in the art, at the time of filing of the application, because it would have been routine to generate polypeptides of at least ten or fifteen amino acids for testing, and there were *in vitro* and *in vivo* assays for the assessment of toxicity. Generation of vectors for the synthesis of recombinant polypeptide fragments for testing would also have been routine. The specification provides ample direction for such recombinant techniques at pages 18 to 38. The "Declaration," at ¶ 10, also attests to the routine nature of generating polypeptide fragments for testing. The "Declaration," at ¶ 11 through ¶ 13, also attests to the routine nature of distinguishing cytotoxic from non-cytotoxic fragments for the CT, CAI, and heat shock proteins, using *in vitro* and *in vivo* assays for the assessment of toxicity.

Applicants also assert that, contrary to the assertions of the Examiner, the specification does provide enablement for the claimed methods of treating an individual infected with *H. pylori*. Applicants have provided ample information on the various aspects for the therapeutic (as well as prophylactic) use of the *H. pylori* component vaccines of the claimed invention. The specification describes pharmaceutically acceptable carriers and adjuvants (page 39, line 4 - page 40, line 15) and vaccine formulations (page 40, lines 16 - 28), and provides guidance with respect to dosage (page 40, line 30 - page 41, line 7) and administration routes (page 41, lines

8 - 17). Furthermore, the evidence of Ghiara *et al.*, 1997, *Infect. Immun.* 65:4996-5002 (Exhibit F), provided with the "Declaration," at ¶ 17, demonstrates that *H. pylori* vaccines comprising CAI polypeptides can be used to treat *H. pylori* infection.

Applicants respectfully submit that the Examiner has not met the "burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. §2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510,1513 (Fed. Cir. 1993). Assuming, arguendo, that the Examiner has met her burden, the "Declaration" rebuts it.

As noted above, the legal standard for enablement is whether the specification provides enough guidance to one skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). A properly supported showing that the disclosure entails undue experimentation is part of the Examiner's initial burden under §112, first paragraph. *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). Determining whether experimentation is undue is driven by a standard of reasonableness for each case, and "a considerable amount of experimentation is permissible . . . if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (B.P.A.I. 1986).

The specification is sufficient to enable those skilled in the art to practice the claimed invention without undue experimentation. Applicants respectfully request that the rejection of claims 42 - 65 under 35 U.S.C. §112, first paragraph be withdrawn. Patentability is determined based on the record as a whole, and factual evidence presented in declarations must be considered. *In re Alton*, 37 U.S.P.Q.2d at1583. Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2), if this rejection is maintained.

Rejections under 35 U.S.C. §102

Under 35 U.S.C. § 102, the standard for anticipation is strict identity. A rejection based on anticipation requires a showing that each limitation of the claim be found within a single

reference (*Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984)), either expressly or inherently. *Glaxo Inc. v. Novopharm Ltd.*, 34 U.S.P.Q.2d 1565,1567 (Fed. Cir. 1995).

The Examiner has rejected claims 38, 39, 42 - 50, and 54 - 56 under 35 U.S.C. §102(a) as allegedly being anticipated by Cover *et al.* (1990). Applicants respectfully traverse this rejection.

The claims, as amended, are directed to (1) purified *H. pylori* CAI polypeptides, (2) *H. pylori* CAI polypeptides comprising at least ten or at least fifteen amino acids, capable of inducing the production of anti-*H. pylori* antibodies, and exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, and (3) vaccines comprising an immunologically effective amount of a *H. pylori* CAI polypeptide comprising at least ten or at least fifteen amino acids, capable of inducing the production of anti-*H. pylori* antibodies, and exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

Cover *et al.* (1990) is a study of the reactivity patterns to *H. pylori* proteins in the sera of human patients with *H. pylori* infection and varying degrees of disease symptoms. In the study, certain patient sera samples were found to contain antibodies reactive with a 128 kDa protein associated with cytotoxic strains of *H. pylori*.

Applicants respectfully disagree with the position of the Office. Contrary to the assertions of the Examiner, Cover *et al.* (1990) did not purify the CAI protein of *H. pylori*. It is Applicants' position that the band in Cover *et al.* (1990), representing the 128 kDa protein, as visualized by immunoblotting with human sera, is <u>not</u> a purified protein. Those skilled in the art know that proteins visualized in immunoblots are not in a purified state; such proteins can be surrounded by and in contact with hundreds of other proteins and contaminants. This position is supported by the "Declaration," at ¶ 22 and ¶ 23.

Even if the 128 kDa protein of Cover *et al.* (1990) is the CAI protein of the claimed subject matter, the failure of Cover *et al.* (1990) to purify the 128 kDa protein renders all claims directed to CAI polypeptides, as amended, novel over Cover *et al.* (1990).

Furthermore, Cover *et al.* (1990) also does not anticipate claims directed to polypeptides of SEQ ID NO:5 CAI, because SEQ ID NO:5 was cloned from a different strain of *H. pylori* (strain CCUG 17874 (*see* page 49, line 1 of specification)) than those in which Cover *et al.* (1990) detected the 128 kDa protein (strain 60190 (*see* Cover *et al.* (1990) Figure 4)).

Cover *et al.* (1990) does not teach or disclose a vaccine of any kind, much less one comprising an immunologically effective amount of a *H. pylori* CAI polypeptide comprising at least ten or at least fifteen amino acids, capable of inducing the production of anti-*H. pylori* antibodies, and exhibiting no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity. As explained in the "Declaration," at ¶ 15 and ¶ 25, a vaccine requires demonstration of a prophylactic or therapeutic effect. Cover *et al.* (1992) does not disclose a protective or therapeutic effect.

To summarize, Cover *et al.* (1990) did not purify the128 kDa *H. pylori* protein that was recognized by antibodies in human sera, thus, the reference neither teaches nor discloses purified CAI protein. Furthermore, Cover *et al.* (1990) does not teach or disclose a vaccine.

Because, Cover *et al.* (1990) does not disclose or teach all of the limitations of the claimed invention, Applicants respectfully request that the rejection of claims 38, 39, 42 - 50, and 54 - 56 under 35 U.S.C. §102 be withdrawn.

Rejections under 35 U.S.C. §103

To support a conclusion that a claimed combination is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed combination or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention obvious in light of the teachings of the references. The Examiner is prohibited

from basing an obviousness rejection on hindsight reconstruction that includes knowledge gleaned only from the Applicants' disclosure. *In re McLauglin*, 170 U.S.P.Q. 209, 212 (C.C.P.A. 1971).

To support a *prima facie* case of obviousness, the Examiner must meet three basic criteria.

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2142.

Obviousness cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Fine*, 5 U.S.P.Q.2d (Fed. Cir. 1988). The question is whether the prior art supplies some motivation or incentive to one of ordinary skill in the art to arrive at the invention as claimed. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1929 (Fed. Cir. 1988). Moreover, the teaching or suggestion supporting the desirability or the combination must be found in the prior art, not in applicant's disclosure. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992).

Applicants respectfully submit that the Examiner has failed to meet the criteria needed to support a *prima facie* case of obviousness. The Examiner has failed to provide a suggestion or motivation to modify the reference she cites. The Examiner has failed to provide a reasonable expectation of success. Finally, the reference fails to teach all the claim limitations. As the three basic criteria to support a *prima facie* case of obviousness have not been supplied, Applicants respectfully submit that the obviousness rejections are improper and should be withdrawn.

The Examiner has rejected claims 60 and 62 under 35 U.S.C. §103(a) as allegedly being obvious in view of Cover *et al.* (1990). Applicants respectfully traverse this rejection.

Claim 60, as amended, is directed to a method of preparing a prophylactic or therapeutic vaccine, comprising bringing into association a polypeptide of CAI, that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, with a pharmaceutically acceptable carrier. Claim 62 is directed to a method of preparing a prophylactic or therapeutic vaccine, comprising bringing into association a CAI polypeptide of SEQ ID NO:5, that is at least ten amino acids in length, can induce the production of antibodies to *H. pylori*, and exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity, with a pharmaceutically acceptable carrier.

As explained above, Cover *et al.* (1990), does not disclose a purified 128 kDa protein, nor does it disclose a 128 kDa polypeptide having all of the claimed characteristics of the CAI polypeptides of the claimed methods of preparing a vaccine. As also explained above, while Cover *et al.* (1990) *does* disclose the immunization of rabbits with preparations of *H. pylori* components to generate antisera, Cover *et al.* (1990) does **not** disclose a vaccine. The Examiner acknowledges, at page 5 of the Official Action, that Cover *et al.* (1990) also "does not teach the inclusion of a pharmaceutically acceptable carrier." The Examiner further alleges, at page 5, that "it was notoriously well known in the prior art to dilute a purified protein in an aqueous medium which would be an inherently pharmaceutically acceptable carrier." Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2) supporting this allegation.

First of all, an "aqueous medium" is <u>not</u> "an inherently pharmaceutically acceptable carrier." As explained at page 39, lines 3 - 17 of the specification, pharmaceutically acceptable carriers are typically large macromolecules used in combination with the antigens of a vaccine. In addition, to being pharmaceutically acceptable, such carriers must not induce the production of harmful antibodies. Without any further explanation of what an "aqueous medium" contains, it

would be incorrect to label an "aqueous medium" as an "inherently pharmaceutically acceptable carrier."

Secondly, regardless of any allegation of what was notoriously well known in the art about diluting purified proteins, the Examiner has failed to set forth any motivation for one of skill in the art to combine a pharmaceutically acceptable carrier with any of the preparations of Cover *et al.* (1990) to supposedly yield the claimed invention.

M.P.E.P. § 2142 states that the Examiner "bears the initial burden of factually supporting any *prima facie* conclusions of obviousness." The Examiner is required to provide more than general assertions that the modifications are within the ordinary skill of the art. Bare statements that the claimed invention is within the capability of a skilled artisan are not sufficient to establish such a *prima facie* case of obviousness. M.P.E.P. § 2143.01.

The Examiner apparently concludes, at page 6 of the Official action, that a *prima facie* case for obviousness is established based on the allegation that "the inoculum used for immunization [by Cover *et al.* (1990)] would inherently contain a pharmaceutically acceptable carrier." The "Declaration," at ¶ 27, explains that three types of *H. pylori* preparations were utilized by Cover *et al.* (1990) to generate antisera in rabbits, and that none would be considered to inherently contain a pharmaceutically acceptable carrier.

Applicants respectfully request that the rejection of claims 60 and 62 under 35 U.S.C. §103 over Cover *et al.* (1990) be withdrawn.

Conclusion

Applicants respectfully submit that claims 38 - 65 are in condition for allowance. A notice of allowance is earnestly solicited. If the Examiner feels a telephonic interview would be helpful, she is asked to call the undersigned at 215-557-5901.

Correspondence

Applicants would like to bring to the attention of the Examiner, the Change of Correspondence Address that was filed in this case on May 22, 2000. All correspondence from the Patent and Trademark Office concerning this application is to be sent to:

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Respectfully submitted,

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